EVALUATION OF COPPER, ZINK AND MAGNISIUM IN CERTAIN CHRONIC PROBLEMS

Muzahim Alkabban*

Faculty of Medicine and Health Sciences / University of Taiz

*Permanent address : University of Baghdad / College of pharmacy.

Abstract:

Serum copper, zinc and magnesium levels were measured in 50 individuals suffering from hypertension, diabetes mellitus, chronic renal failure and laryngiocarcinoma, as 10 patients for each disease, with 10 normal control. Patients and control were chosen at a nearly same ages in order to reduce the variation in the element ranges.

Significant decrease in serum copper concentration ($P < 0.05$) occurred for the hypertensive patients (110.3 ± 33), and a highly significant increase in serum copper concentration ($P < 0.01$) was noticed for carcinoma patients (172.2 ± 13), when each compared with the control copper concentration (140 ± 20). Moreover, there were non significant increase in copper concentrations of diabetic and chronic renal failure patients (160.8 ± 33), (154.7 ± 36) respectively , ($P > 0.05$), when compared with control copper.

Significant increase was noticed in serum zinc concentration of the patients with hypertension (147.1 ± 38), ($P < 0.05$), and a highly significant decrease appear ($P<0.01$) in serum zinc concentration of carcinoma patients (59.6 ± 9), when they were compared with control zinc (110 ± 6). But no significant changes ($P > 0.05$) occurred for zinc concentrations of diabetic and chronic renal failure patients (115.9 ± 48.5), (101.5 ± 50) respectively, when each compared with control zinc.

No significant changes ($P > 0.05$) noticed in serum magnesium concentrations of all patients in the four groups (hypertension, diabetes mellitus, chronic renal failure and carcinoma), (1.73 ± 0.33),(1.76 ± 0.31),(1.98 ± 0.35), (1.74 ± 0.26) respectively, when each compared with control magnesium (1.80 ± 0.12).

Introduction:

Trace elements are found only in minute quantities in the body, but they are essential elements required for life. Absence of these elements result in death or a severe malfunction of the organism, and physiological amounts of only these elements prevent or alleviate the impairment. Most essential trace elements or so called micronutrients function, as an enzyme cofactor or act as an enzyme activator [1].

Copper (Cu) is one of the important trace elements present in the muscle, bones and liver as 90% of its total body concentration. Copper is required in the formation of hemoglobin, red blood cells and bones, while it helps in the formation of elastin as well as collagen; making it necessary for wound healing. It is important in iron metabolism, and its deficiency impair iron absorption, leading to anemia, osteoporosis, thinning of bones, thyroid gland dysfunction, heart diseases as well as nervous system problems [1,2,3]. Copper is a metalloprotein involved in oxidation-reduction reactions as it is an integral component of many metalloenzymes such as ceruloplasmin which contains over 90% of plasma copper, cytochrom c oxidase and superoxide dismutase [2]. Copper was found to be significantly increased in the plasma of myocardial infarct patients, moreover, strong evidence indicates that high plasma copper levels may be associated with heart failure and rhythm disorders [4]. Although, it was reported that humans fed diets believed to be marginal in copper have exhibited many symptoms closely related to those of coronary heart disease, include abnormal electrocardiograms, hypercholesterolemia , glucose intolerance and hypertension [5].

Zinc (Zn) is second to iron as the most abundant trace element in the body. So, it has such a wide application in human health that everybody should insure that he obtains enough of this humble trace element. Present in prostate, semen, liver, kidney, retina, bones and muscles[1,2]. Zinc is essential component of many metalloenzyme such as carbonic anhydrase, alkaline phosphatase, RNA and DNA polymerase; as it is involved in the active site of the related enzymes[6,7]. It is important in protein synthesis and in gene expression as well as it is necessary for a healthy immune system. Zinc is important for cell division and necessary to be at the top form in the hair, nails and skin[8,9,10]. Zinc deficiency occurs in patients with renal diseases has

been attributed to loss of protein-zinc complexes in proteinuria or to decreased tubular reabsorption of zinc. Furthermore zinc deficiencies in patients with neoplasm have been reported as an increased in tissue catabolism and increased urinary excretion of zinc[1]. Plasma zinc levels are significantly elevated in type-1 diabetes mellitus patients, while plasma copper and magnesium levels are not significantly altered[11].

Magnesium (mg) is considered to be a trace element, even it is the fourth most abundant cation in the body and second to potassium within the cell. It competes with calcium for binding with protein and form chelates with important intracellular anionic ligandins, notably adenosine triphosphate (ATP)[12]. Magnesium effects enzyme activity by binding the active site of some enzymes as pyruvate kinase and enolase through the regulation of Na-K-ATPase activity[1]. Several in vitro and in vivo studies have demonstrated that insulin may modulate the shift of magnesium to intracellular space. The poor intracellular magnesium level as noticed in non-insulin- dependant diabetes mellitus and in hypertensive patients may result in a defective of tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration[13]. Several related cardiac problems have been linked to magnesium depletion, such as hypertension, myocardial infarction, cardiac dysrhythmias, coronary vasospasm, and premature atherosclerosis[1]. However, Diabetes mellitus is the most common pathological state in which secondary magnesium deficiency occurs and its abnormal metabolism vary according to the different clinical form of diabetes[14].

The recorded adults normal reference ranges for copper from 70 to 155 µg/dl., for zinc from 70 to 120 µg/dl., and for magnesium from 1.6 to 2.6 mg/dl [1].

Flam atomic emission or absorption spectrophotometry techneque is used for the analysis of patient samples. It is quick and accurate, besides offering good specificity and sensitivity, moreover, it is widely used in hospital laboratories as relatively simple to operate[15,16].

Materials and Methods:

This study is done on five groups of adult people, each of them involves 10 individuals with the following characters:

Group I : Involves 10 adult normal control individuals (5 females and 5 males) of 40

to 65 years old, free of any chronic problem.

Group II : Involves 10 adult hypertensive patients (6 females and 4 males) of 41 to 84 years old.

Group III: Involves 10 adult diabetic patients (6 females and 4 males) of 22 to 60 years old.

Group IV: Involves 10 adult patients with chronic renal failure (5 females and 5 males) of 39 to 65 years old.

Group V: Involves 10 adult patients with laryngiocarcinoma (3 females and 7 males) of 27 to 51 years old.

All the groups, patients and control were on their normal traditional diet, except for sodium restriction in those with persistent hypertension. They were all on their own related therapy, but non of these drugs reported to be affecting serum copper, zinc and magnesium. Five milliliters of blood sample were collected from each patient in a test tube, then serum was prepared from each sample for Cu, Zn, and Mg measurements.

Atomic absorption spectrophotometry (AAS) was the method used for the estimation of the above trace element levels in the serum of control and diseased patients, by a shimatzu machine model (AA670 flamed electrothermal AAS). The optimum conditions used for determination of these trace elements are outlined in Table I, and all chemicals used in this study were analar grade.

Table 1: shows the optimum conditions which were used for determination of copper, zinc and magnesium with a gas flow (Air / C_2H_2) for all three elements.

ELEMENT	GAS FLOW RATE (cm^3 / min.)	WAVE LENGTH (nm)	HCL LAMP CURRENT (pulse / sec.)	SLIT EDTH (nm)
Zn	2.0	213.9	4	1.5
Cu	1.8	324.8	3	0.5
Mg	2.0	271.0	3	0.1

Results:

Results of atomic absorption spectrophotometry for the concentrations of copper, zinc and magnesium measured in this study are demonstrated in Table 2 and figures 1 and 2. This table and figures show the changes in the levels of these three trace element concentrations in the four diseased groups (hypertensive, diabetic, chronic renal failure and carcinoma), in comparison with control group.

There is a highly significant increase ($P < 0.01$) in serum copper concentration of carcinoma patients (172.2 ± 13), and significant decrease noticed ($P < 0.05$) in serum copper concentration of patients with hypertension (110.3 ± 33), when each compared with control copper (140 ± 20). But, non significant increase occurred ($P > 0.05$) for copper concentration of patients with diabetes mellitus (160.8 ± 33), and patients with chronic renal failure (154.7 ± 36), when each compared with copper control.

There is a significant increase ($P < 0.05$) in serum zinc concentration of patients with hypertension (147.1 ± 38), and a highly significant decrease ($P < 0.01$) occurred for zinc concentration of laryngiocarcinoma patients (59.6 ± 9), when each compared with control zinc (110 ± 6). But, no significant changes occurred for zinc levels in patients with diabetes mellitus (115.9 ± 48.5), and chronic renal failure patients (101.5 ± 50), $P > 0.05$, when they were compared with the control zinc.

Non of the four clinical problems (hypertension, diabetes mellitus, chronic renal failure and laryngiocarcinoma) showed a significant changes in magnesium concentrations (1.73 ± 0.33), (1.76 ± 0.31), (1.98 ± 0.35) and (1.74 ± 0.26) respectively, when each compared with the control magnesium (1.80 ± 0.12), ($P > 0.05$). However, there is slightly increase in mean magnesium concentration of chronic renal failure patients as compared with control magnesium.

Statistical results are demonstrated in Table 3 for the above measurements using test for the difference of means by Epidemiological Data Analysis Tables (EPIDAT).

Table 2 : Shows the mean ± SD of serum copper, zinc and magnesium concentrations in control and four different diseases(hypertension, diabetes mellitus, chronic renal failure and carcinoma). Ten patients used in each group.

GROUPS	Copper µg/dl.		Zinc µg / dl.		Magnesium mg / dl.	
	Mean	SD	Mean	SD	Mean	SD
CONTROL	140.0	20	110.0	6.0	1.80	0.12
HYPERTENSIVE	* 110.3	33	* 147.1	38.0	1.73	0.33
DIABETIC	160.8	33	115.9	48.5	1.76	0.31
CHRONIC RENAL FAILURE	154.7	36	101.5	50.0	1.98	0.35
LARYNGIO CARCINOMA	** 172.2	13	** 59.6	9.0	1.74	0.26

* Means significant result.

** Means highly significant result.

Table 3 : Shows test of P-value for the difference of means according to EPIDAT of serum copper, zinc and magnesium measurements in the four groups of patients (hypertensive, diabetic, chronic renal failure and carcinoma), as compared with their related controls.

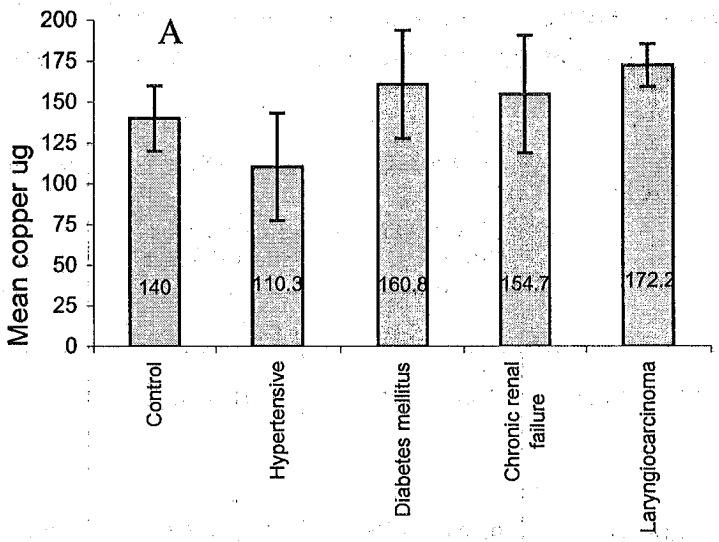
GROUPS	COPPER	ZINC	MAGNESIUM
	P-value for the difference of means	P-value for the difference of means	P-value for the difference of means
HYPERTENSIVE	* 0.02 < 0.05	* 0.01 < 0.05	0.54 > 0.05
DIABETIC	0.105 > 0.05	0.71 > 0.05	0.71 > 0.05
CHRONIC RENAL FAILURE	0.27 > 0.05	0.606 > 0.05	0.152 > 0.05
LARYNGIO CARCINOMA	** 0.0005 < 0.01	** 0.00001 < 0.01	0.52 > 0.05

* **Means significant result.**

** **Means highly significant result.**

EPIDAT: Means Epidemiological Data Analysis Tables.

Figure 1: Shows the means ± SD of serum copper (A) and serum zinc (B) in control, hypertensive, diabetic, chronic renal failure and carcinoma patients (source table 2)


A
Mean copper ug
200
175
150
125
100
75
50
25
0
140
110.3
160.8
154.7
172.2
Control
Hypertensive
Diabetes mellitus
Chronic renal failure
Laryngiocarcinoma

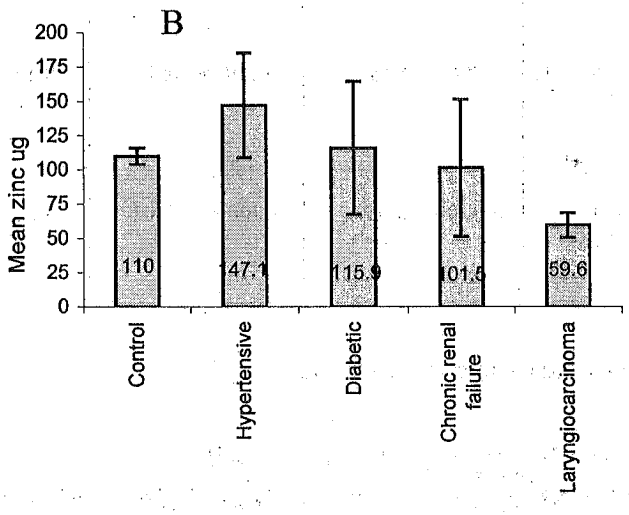
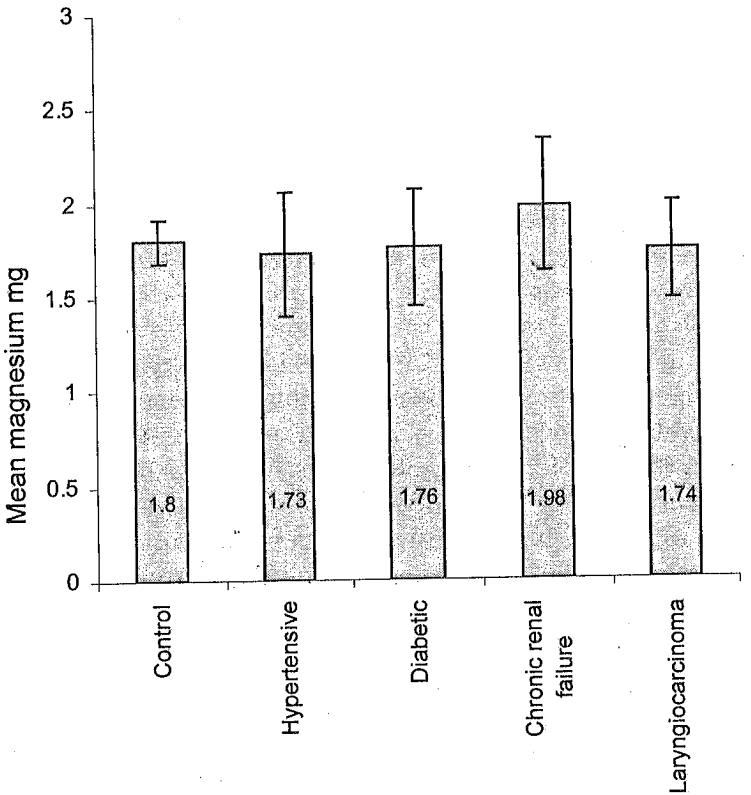

B
Mean zinc ug
200
175
150
125
100
75
50
25
0
110
147.1
115.9
101.5
59.6
Control
Hypertensive
Diabetic
Chronic renal failure
Laryngiocarcinoma

Figure 2: Shows the means ± SD of serum magnesium in control, hypertensive, diabetic, chronic renal failure and carcenoma patients (source table 2).



Discussion:

The quantities of trace elements in which they are found in the body are so small, that they can only be detected by spectrographic methods or by using radioactive elements, so the interrelation of these micronutrients are difficult to study, since they are found occurring

together in various forms and amounts in the diet. Their absorption from the intestinal tract may be dependant on their relative concentrations, which might be synergetic or antagonistic, and the amount could depend on the amount of other essential trace elements in the diet[17]. Several attempts have been done to find the changes in the levels of these elements in different diseases. Cooper, zinc and magnesium as micronutrients are suspected to have a role in pathogenesis and prognosis of diabetes mellitus, coronary heart disease, hypertension, renal diseases, neoplasm and inflammatory diseases[1,11,13,18].

This study shows that there is a significant decrease in serum copper concentration of patients with hypertension and a highly significant increase in serum copper concentration of patients with laryngiocarcinoma, but, a non significant increase noticed in diabetic and chronic renal failure patients, when they were compared with control copper (Tables: 2 and 3), and figure 1A. The highly significant increase of serum copper in carcinoma patients is considous with the increasing of tissue mass in case of tumor, as the main function of copper metalloproteins involves oxidation-reduction reactions. Furthermore most of the copper containing enzymes bind and react directly with molecular oxygen specially in the active growing tumor tissue[1]. Moreoever, it was noticed that humans fed diets believed to be marginal in copper have exhibited many symptoms closely related to those of coronary heart diseases, including glucose intolerance, and hypertension[5], which may support the above result of hypertensive patients. While Zagar, et al. concluded that there was no significant changes in cooper concentration occur for patients with type-1 diabetes mellitus[11], so, the non significant increase noticed in this study agree with such conclusion. Moreover, changes of the ceruloplasmin during renal diseases affect copper in the same level[1], and this study indicates this finding.

There is a significant increase in serum zinc concentration in hypertensive patients, with a highly significant decrease of serum zinc concentration in patient of laryngiocarcinoma , but no clear changes occur for zinc concentrations in diabetic and chronic renal failure patients (Tables: 2 and 3) and figure 1B. Most of the clinical significance related to zinc levels in the body are due to its deficiency rather than its increase. So, the highly significant decrease in serum zinc concentration in the carcinoma patients may be attributed to anorexia, starvation, loss zinc from the catabolized tissue and / or due to the long

term effect of interleukin-1 in case of chronic condition toward low body zinc through hyperzincuria[1]. While the occurrence of zinc deficiency in patients with renal disease has been attributed to loss of protein-zinc complexes in proteinuria or to decreased reabsorption of zinc, depending on the severity of the disease[1,19]. Furthermore, diabetes mellitus is one of the diseases at which mild or no zinc deficiency occurs [20], however, Zargar, et al. concluded that plasma zinc levels are significantly higher in type-1 diabetes mellitus patients[11]. No clear reasons for zinc increase in hypertensive patients, so, I can say it might be due to the use of diuretics and reduced volume of distribution, which may lead to elevation of zinc levels.

This study also shows slightly non significant increase in serum magnesium concentration of the patients with chronic renal failure, but no clear changes occur for other three conditions in the magnesium concentrations of patients with (hypertension, diabetes mellitus and carcinoma), when each compared with control magnesium (Table: 2 and 3) and figure 2. Conditions of renal failure associated with glomerular filtration as uremia, result in retention of magnesium and hence elevation of its serum concentration, however, these patients used potassium sparing diuretic (Triametren), in result is magnesium sparing too[1]. Therefore, in some circumstances it was noticed that chronic latent magnesium deficiency has been linked with several diseases as cancer and hypertension , moreover the poorly controlled diabetes mellitus increases loss of magnesium in urine causing depletion of magnesium stores [1,13,14].

In conclusion, levels of different trace elements in the body changed according to the type and severity of the chronic disease, keeping in mind the effect of medicine used by the patients, but, do not forget their nutritional status.

References:

1. Burtis, C.A. and Ashwood, E.R., Eds.: Tietz Textbook of Clinical Chemistry. 3rd ed. Philadelphia, Pennsylvania, W.B. Saunders Co., 1999. PP. 1029 – 1055.
2. Laker, M.F. Clinical Biochemistry for Medical Students. W.B. Saunders Co., Ed. London, 1996, pp. 66 – 67.

3. Champe, P.C. and Harvey, R.A., Lippincott's Illustrated Reviews: Biochemistry. 2nd edition. J.B. Lippincott Co. 1994, P. 307.
4. Painter, F. M., Trace elements in prognosis of myocardial infarction and sudden coronary death. J. Trace Elements in Expe.Med.,1996, 9/2, 57 – 62.
5. Klevay, L.M., Ischemic heart disease: Toward a unified theory. In: Role of Copper in Lipid Metabolism. K.Y. Lei, T.P. Carr, Eds. Boca Raton, FL, CRC Press, 1990, pp. 233 –267.
6. Marie-Helene, L.D. and Luis, M.J., Structural evidence of functional divergence in human alkaline phosphatase., J. Biol. Chem., Dec. 2002, 277, 49808 – 49814.
7. Magnusson, P., Larsson, L., Magnusson, M., et al., Isoforms of bone alkaline phosphatase characterization and origin in human trabicular and cortical bone., J. Bone Miner. Res. Nov. 1999, 14(11): 1926 – 33.
8. Choo, Y., Klug, A., Physical basis of a protein-DNA recognition code., Curr. Opin. Struct. Biol., 1997, 7, 117 – 125.
9. Klug, A. and Schwabe, J.W., Protein motifs 5. Zinc fingers. FASEB. J., 1995, 9, 597 – 604.
10. Shi, Y., Berg, J.M., DNA unwinding induced by zinc finger protein binding. Biochemistry, 1996, 35, 3845 – 3848.
11. Zargar, A.H., Bashir, M.I., Masoodi, S.R., et al.: Copper, zinc and magnesium levels in type-1 diabetes mellitus. Saudi Med J., 2002; 23(5): 539 – 42.
12. Ryan, M.F., The role of magnesium in clinical biochemistry: an overview. Ann. Clin. Biochem., 1991, 28, 19 – 26.
13. Painter, F. M., Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium. Am. J. Hypertens, Mar. 1997, 10(3): 346 – 55.
14. Painter, F. M., Magnesium and potassium in diabetes and carbohydrate metabolism. Review of the present status and recent results. Magnesium, 1984, 3(4-6): 315 – 23.
15. Dean, J. R., Ando, D. J., Metcalfe, E., Atomic absorption and plasma spectroscopy. New york, John Wiley and Sons, 1997.
16. Jackson, K. W., Mahmood, T.M., Atomic absorption, atomic emission, and flame emission spectrometry. Anal. Chem., 1996, 68: 231R – 256R.

17. Klevay, L. M.,Diatary cooper and risk of coronary heart disease. Am. J. Clinical Nutrition, 2000; 71(5): 1213 – 1214.
18. Satur, C. M. R., Stubington, S. R., Jennings, A., et al., Magnesium flux during and after open heart operations in children. Ann. Thorac. Surg., 1995, 59(4): 921 -927.
19. Baynes, J. and Dominiczak, M. H., Medical biochemistry. Eds: Louise Crown. Published by Mosby. 1999, P. 121 – 122.
20. Braunwald, E., Fauci, A. S., Kasper, D. L., et al. Eds.: Harrison's principle of internal medicine. 15th ed. 2001, P. 468.